CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date below:

7/30/02 Juanita A. Rangel
Date Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Stanislaw R. Burzynski

Serial No.: 09/603,320

Filed: June 26, 2000

For: PHENYLACETIC ACID COMPOSITIONS FOR TREATING OR PREVENTING HYPERCHOLESTEROLEMIA

Confirmation No.: 3169

Group Art Unit: 1617

Examiner: BAHAR, M.

Atty. Dkt. No.: 10379.0046.NPUS00
(BURG046---)

REPLY BRIEF TO EXAMINER'S ANSWER DATED JUNE 5, 2002

BOX AF
Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant hereby submits this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer mailed June 5, 2002.

It is believed that no fees are required in association with this filing, however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-2508/**10379.0046.NPUS00**.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

RESPONSE TO EXAMINER' ANSWER

I. Lines 18-23 of page 3 of the specification must be viewed in light of lines 23-28 of page 3 and in view of Applicant's explanation

The Specification for the instant application recites *inter alia* that:

> [i]t has been known for some time that compounds such as 3-phenylacetylamino-2,6-piperidinedione and its hydrolysis products, such as phenylacetic acid, and salts, precursors, and analogs thereof (together, "3-phenylacetylamino-2,6-piperidinedione and its derivatives"), can block the formation of iso-pentenylpyrophosphate from 5-pyrophosphomevalonate, a reaction in the pathway of cholesterol biosynthesis; as a result, these compounds may lower serum cholesterol levels. **Therefore, it was desirable to determine which, if any, of 3-phenylacetylamino-2,6-piperidinedione and its derivatives can lower serum cholesterol levels, and thus can form the basis of a pharmaceutical composition useful in treating or prevent hypercholesterolemia.** Derivatives of 3-phenylacetylamino-2,6-piperidinedione that exhibit such activity are disclosed herein.

See, Specification page 3, lines 18-28, (emphasis added).

Applicant asserts that the Examiner has clearly misinterpreted this passage. It is the Examiner's position that the phrase "it has been known for some time" stands by itself to prove that the statement which follows is an admission that as to what is prior art. In characterizing the passage thusly, the Examiner explicitly asserts that context and grammar are to be ignored in determining the meaning of the phrase (*see* Examiner's Answer, page 5, last paragraph). The Examiner's meaning for the phrase "it has been known for some time" can supported only if that phrase is interpreted, in a vacuum, with complete disregard for both grammar and context (that is by ignoring the sentence's punctuation, the content of the two succeeding two sentences, and the clear intent of the entire specification).

At page 5 of the Examiner's reply the Examiner states that "[g]iven that applicant and/or his representative draft the specification, they are best able to disclose the novel and unobvious characteristics of the invention. . ." Applicant wholeheartedly agrees. This is precisely what Applicant has done by indicating that Applicant's purpose for the work was to discover which if

any of the described compounds could be used in novel treatment methods to effectively treat, *inter alia*, hypercholesterolemia.

While Applicant is free to describe his invention as he sees fit, the Examiner is not free to ignore any part of that description. Nevertheless, the Examiner has failed to respond when Applicant has directed attention to the passage which recites "[t]herefore, it was desirable to determine which, if any, of 3-phenylacetylamino-2,6-piperidinedione and its derivatives can lower serum cholesterol levels, and thus can form the basis of a pharmaceutical composition useful in treating or prevent hypercholesterolemia." The Examiner presents no explanation or evidence which harmonizes her position with a plain, reading of the this sentence, instead the Examiner has consistently ignored this sentence in her arguments. Applicant contends that the reason for this is that the Examiner's position is inconsistent with the plain meaning of the paragraph, when taken as a whole. If, in fact, it were known, as asserted by the Examiner, that the described compounds inhibited hypercholesterolemia, there would be no need to find out "*which, if any*," of the compounds would be effective. Thus, the interpretation offered by the Examiner is inconsistent with and refuted by a contextual reading of page 3, lines 18-28 of the specification.

In contrast, Applicant's position is fully consistent with a plain reading of the entire paragraph. As indicated at page 11 of the Appeal Brief, the phrase "[i]t has been known for some time that compounds such as3-phenylacetylamino-2,6-piperidinedione and its hydrolysis products...can block the formation of iso-pentenylpyrophosphate from 5-pyrophosphomevalonate" is simply a summarization of the Castillo *et al* reference (*Neurochem. Int.* 18:171-174 (1991), a copy of which was submitted with the Appeal Brief) which teaches the *in vitro* inhibition of mevalonate 5-pyrophosphate decarboxylase. It has been Applicant's consistent and unwavering position that there was no teaching or suggestion that any of the compounds described in the present application would inhibit hypercholesterolemia.

The passage which recites "*as a result these compounds may lower serum cholesterol levels. Therefore, it was desirable to determine which, if any,...[of these compounds] can lower*

serum cholesterol levels. . ." makes sense only if viewed as Applicant's statement of the purpose of the work and thus cannot be considered to be prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Therefore, contrary to the Examiner's allegations, Applicant has clearly shown that this statement is not "prior art." In contrast, Examiner proffers nothing beyond conclusory statements regarding the meaning of a single passage, taken out of context. Consequently, the Examiner's position is untenable and should be reversed.

II. Response to obviousness rejection under 35 U.S.C. § 103 as allegedly being unpatentable over Hendry *et al.* (U.S. Pat. No. 5,238,947) and the alleged admission at page 2-3 of the Specification.

A. Response to Examiner's argument regarding motivation to try and reasonable expectation of success.

It is Applicant's unwavering position that the existing prior art, at most, provides motivation for one of ordinary skill in the art to do experimentation to determine whether some of the compounds described in the claimed methods might be effective to treat hypercholesterolemia.

The Examiner has alleged that there is no mention of either "*in vitro* or *in vivo* application or employment of these compounds." Applicant disagrees, the presence of a host and *in vivo* application is clearly implied by the passage reciting that "it was desirable to determine which, if any [of these compounds] can lower serum cholesterol levels. . . ." Serum cholesterol levels can only be lowered through treatment of a host.

Applicant points out that the passage from the biochemistry text was not intended to demonstrate a method for reducing serum cholesterol. Rather, it was intended to show the complex nature of the condition's etiology. As noted by the Examiner, the biochemistry text "teaches [some of] the possible causes" of the disease. This information clearly supports the Applicant's position that, because of the complex etiology of hypercholesterolemia, the mere fact that a compound inhibits the *in vitro* function of one enzyme in the cholesterol synthesis pathway does not make it obvious that the compound will function to inhibit the same enzyme *in vivo*

(other factors present *in vivo*, but not *in vitro*, could interfere with and/or prevent such inhibition). Furthermore, even if the compound were known to inhibit that enzyme *in vivo*, which it was not, this is not a guarantee that it would lower serum cholesterol levels, which are dependent on a multitude of factors.

The Examiner, at page 7 of the Reply, bases this rejection on the premise that the prior art teaches that "3-phenylacetylamino-2,6-piperidinedione and its derivatives [are] known to block a specific step in the cholesterol biosynthetic pathway and in turn block cholesterol synthesis result[ing] in the lowering of blood cholesterol levels". As described above, Applicant has clearly shown that the cited passage is not "prior art" as alleged by the Examiner. At most, it suggests that it was known that certain compounds inhibit a certain enzyme, *in vitro*. Moreover, there is no evidence in the prior art that these compounds could or would inhibit the same enzyme *in vivo*, let alone lower serum cholesterol levels. Therefore, this rejection by the Examiner should be reversed.

B. *In vitro* inhibition of the activity of a single enzyme does not render anti-hypercholesterolemia activity obvious.

The Examiner provides no evidence to support an obviousness rejection of the pending claims. The Examiner's contention is since "3-phenylacetylamino-2,6-piperidinedione and its derivatives" were known to inhibit, *in vitro*, the activity of a single enzyme known to be part of the cholesterol biosynthetic pathway, this renders obvious the use of such compounds to inhibit hypercholesterolemia. To support this position the Examiner alleges that the claims are obvious because "the compound is known to possess the desired activity *in vitro*." Applicant believes that this is the fundamental error in the Examiner's reasoning, that is, it is logically unsound to equate the *in vitro* inhibition of a single enzyme with the *in vivo* treatment of hypercholesterolemia (a complex condition affected by a multitude of factors). Furthermore, contrary to the requirement of *In re Zurko* 258 F.3d 1379, 59 USPQ2d 1693 (Fed. Cir. 2001), the Examiner offers absolutely no objective evidence in support this position. Applicant contends that since there is no objective evidence to support this rejection, the Examiner has merely

offered her opinion, improperly relying on her own "understanding or experience" (*id.*, at 1389), to support the instant rejection under 35 U.S.C. § 103. For these reasons the objection of the claims under 35 U.S.C. §103 is insupportable and should be reversed.

III. CONCLUSION

For all of the reasons explained above, Applicant contends that the Examiner has not established a *prima facie* case for rejection of the appealed claims as being obviousness with respect to the cited art. The Examiner has consistently misinterpreted the specification by ignoring the contextual meaning of the words and has failed to respond to Applicant's arguments regarding this meaning. Additionally, the Examiner has based the present obviousness rejection entirely on the described textual misinterpretation and on her own opinion and understanding, failing, completely, to provide any objective evidence in support of her conclusions. Therefore, Applicant believes that the rejection of the appealed claims, as being obvious under 35 U.S.C. § 103(a), is improper and should be reversed.

Respectfully submitted,

Matthew Madsen

Matthew L. Madsen
Reg. No. 45,594
Agent for Applicant

HOWREY SIMON ARNOLD & WHITE, LLP
750 Bering Drive
Houston, Texas 77057-2198
(713) 787-1400

Date: July 30, 2002